Remarks

In response to the Office Action of January 31, 2005, Applicant notes that the initial three month term for response expired April 31, 2005. A check in the amount of $1,020.00 requesting a three-month extension of time accompanied by a duplicate request for extension is enclosed.

With entry of this Amendment and Response:

- claims 86 to 123, 141 to 143, and 151 to 154 are currently pending in the present patent application, (it being noted that claims 86, 106, 108 to 113, 121 to 123, 141 to 143, and 151 to 154 of which are currently amended); and

- claims 124 to 140, and 144 to 150, are cancelled.

The amendments to the claims are supported throughout the specification, including, but not limited to p.3, l.26 to p.4, l.10 (*in re.* the isolated amino acid sequences of the present invention), and p.5, l.20 *et seq.* (*in re.* isolated anti-Factor VIII allo-antibodies of the present invention).

I. Response to Restriction Requirement:

Applicant notes the Examiner's statement in the Office Action:

"*After further consideration the Examiner will examine claims 86-123, 141-143 and 151-154. Claims 124-140 and 144-150 are withdrawn from further consideration pursuant to 37 CFR 1.142 (b), as being drawn to a non elected invention, there being no allowable generic or linking claim* (...)".

The cancellations have been made herewith to these claims and examination on the remaining claims is respectfully requested.

The Requirements of 35 USC 121 & 372 are thus deemed to be met.

It is respectfully submitted that Applicant reserves the right to file a divisional application(s) for any or all of the remaining Groups of claims as the Law permits.

II. Abstract:

In response to the objections raised to the Abstract, a separate sheet is hereby filed, as well as a copy of the cover page of the PCT Application (as published), from which the instant application is derived.

Should any further amendment to the Abstract be necessary, Applicants undersigned attorney is respectfully requested to be further contacted.

The requirements of 37 CFR 1.72(b) are thus deemed to be met.

III. Amino Acid Sequences:

a) The amino acid sequences on pp.5, 7, 20, claims 111-113, 121-123, and 141-143 (it being noted that claims 135-137 and 148-150 are withdrawn from consideration) have been labelled as to their respective SEQ. ID Nos. Said pages are filed herewith as hand-amended and clean versions.

   The Application is thus deemed to comply with the requirements of 37 CFR 1.821 through to 1.825.

b) With regard to the Examiner's remarks with reference to the specific residues in the sequence of Factor VIII, in that the sequence of this protein is not included in the CRF or written sequences, the Applicant hereby files the written sequence of human Factor VIII.

The requirements are thus deemed to be met.

IV. Figures 1-5:

a) Figures 1-5, filed with the PCT Application are hereby filed as an amendment. Submission of these drawings are submitted not to introduce new matter. The requirements of 35 USC 371 are thus deemed to be met.

b) With regard to the Examiner's comment that there is no recitation of "Figure 3 A-C" in the Brief Description of the Drawings, it is submitted herewith that Figures 3B & 3D refer to Patient "Bor", and Figures 3A & 3C to Patent "Wal". The rest is self-explantory, i.e. that in Figures 3A & 3B, the IgG in nM is given along the abscissa, and the molecular weight in kD is given up the ordinate ; and in Figures 3C & 3D, time is given (mins) along the abscissa, and the molecular weight in kD is given up the ordinate.

It is submitted that such explanations would be completely self-explanatory, in view of the description and the other Figures.

To this end, p.15 of the description as originally filed has been amended accordingly and is filed herewith.

It is submitted that no new matter has been added.

Should there be any question regarding these amendments, the Examiner is kindly requested to telephone applicant's undersigned representative if it is believed that a telephone interview would be beneficial in concluding these matters.

V. <u>Patentability (35 USC 101)</u>:

a) *In re:* claims 111-116, 141-143 and 151-154:

In the Action, it is stated that there must be some indication of the intervention of the "hand of man" in product claims. It is suggested that adding the word "isolated" or a similar term to said claims would overcome his rejection.

Applicant has made such amendments. Said amendments are made herewith to claims 111-113, 121-123, in relation to the isolated amino acid sequences, and to claims 151-154, in relation to the isolated anti-Factor VIII allo-antibody. It is noted that claims 135-137 and 148-150 are withdrawn from consideration.

The requirements of 35 USC 101 are thus deemed to be met.

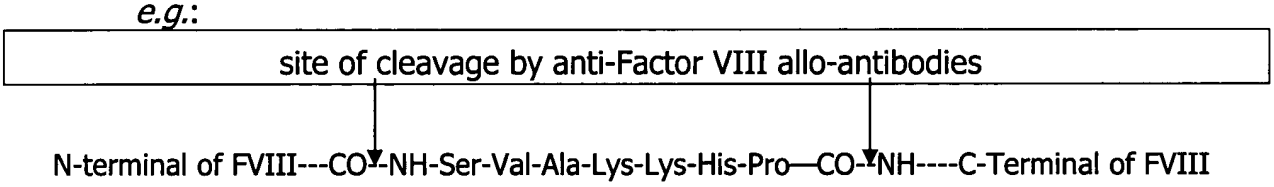
b) *In re:* the three heptapeptide sequences:

With reference to the Examiner's comments following "*the claimed invention is not supported by either a specific or substantial asserted utility or a well established utility*",

the Applicant provides the following submissions:

In response to the Examiner's statement: "*Presumably these are the regions of cleavage of Factor VIII by the allo-antibody of the claims*", the Applicant submits as follows:

It is submitted that the isolated amino acid sequences in question are regions of cleavage of Factor VIII by the allo-antibody of the claims. Namely, said sequences are those found as from the C-terminal of the site of cleavage of the Factor VIII molecule by the anti-Factor VIII allo-antibodies, downstream in the direction of the C-terminal of the Factor VIII amino acid sequence, *i.e. e.g.*:



In response to the Examiner's statement: "*there is not disclosed or asserted any specific or substantial use for these peptides. Presumably if the peptides were added to the Factor VIII/allo-antibody mix they would be cleaved and thus would not be inhibitors of the reaction.*", the Applicant submits as follows:

It is respectfully believed that the Examiner has attention drawn to the fact that with respect, mis-characterized this when one of said peptide sequences is added to the Factor VIII/allo-antibody mix then a "Competitive Inhibition", a term which is well-understood by the person of ordinary skill in the art, ensues; it is due to the competition of these peptides with the corresponding sequences of the Factor VIII molecule to be cleaved, that they thus "prevent" or "protect" the Factor VIII from being cleaved by the allo-antibody. The isolated peptide sequences do not have the cleavage site which is recognised by the allo-antibody, nor do the isolated peptide sequences have bonds which

are susceptible to being cleaved by the allo-antibody, since these isolated peptide sequences are merely the sequences as from the C-terminal of the cleavage site, (Point V. b) *supra*). It is submitted that this is in fact deduction : the inventors have not demonstrated it.

VI. <u>Specification (35 USC 112)</u>:

a) *In re.* claims 111-113:

In response to the Examiner's comments that "*one skilled in the art clearly would not know how to use the claimed invention*". It is respectfully submitted in response that were the person skilled in the art told the above, in Point V. b), *supra*, in particular, then he would know that the fragments would enter into competitive inhibition with the Factor VIII molecule, thus "preventing", or "protecting" the Factor VIII molecule from being cleaved by the allo-antibody.

b) i) *In re.* claim 86:

In response to the Examiner's statement that "*claim 86 is confusing and indefinite in the recitation of "said Factor VIII has effectively been degraded..." on lines 8-9*", it is respectfully submitted that it is in fact meant that "any degradation that can be shown", as the Examiner suggests.

Consequently, the word "effectively" has been removed from the claim 86, in thus dispelling any confusion generated thereby.

The Examiner is thanked for bringing this to the Applicant's attention.

b) ii) *In re.* claims 106, 108 and 109:

In response to the Examiner's objection that claims 106, 108 and 109 are indefinite in the recitation of "such as", it is respectfully submitted that "such as", is simply illustrative.

The recitation has been deleted in all claims 106, 108 and 109.

The Examiner's objection is deemed to be overcome.

b) iii) *In re.* claim 110:

In response to the Examiner's objection that claim 110 is indefinite in the recitation of "said sequencing", the antecedent claim number has been corrected to read 105.

The Examiner's objection is thus deemed to be overcome.

c) *In re.* claims 114-116, 121-123 and 141-143 (35 USC 112):

With regard to claims 114-116, with regard to the enablement requirement, *i.e.* subject matter described in the specification in such a way as to enable one skilled in the art to make the invention, it is submitted to the Examiner that the preparation of the heptapeptides in question would be common knowledge to the person skilled in the art of organic chemistry, particularly of peptide synthesis.

It is furthermore given, in the description, p.6, l.5 *et seq.*, a definition of such an analogue, this definition being deemed to easily enable such a person skilled in the art to make the invention.

VII. <u>Novelty (35 USC 102)</u>:

a) *In re.* claims 111-113:

Applicant has carefully reviewed documents A (US 5,744,326 (Ill *et al.*)), B (US 5,744,446 (Lollar *et al.*)), and C (US 5,869,292 (Voorberg *et al.*)), cited by the Examiner, and it is his understanding at this time that the sequences of documents A, B, and C cited are <u>not</u> isolated as are the heptapeptide sequences of the present invention, *i.e.* the heptapeptides of the present invention are <u>isolated</u>, discreet molecules the N-terminus of which is a primary NH_2 group, and the C-terminus of which is a –COOH group, unlike the <u>non-isolated</u> protein sequences of documents A, B & C, above, wherein said groups are present as an amide, -NHCO-, group in a chain.

The addition of the word "isolated" to said claims of the present patent application should make this clear to the person skilled in the art.

b) *In re.* claims 151-154: claims to "an isolated anti-Factor VIII allo-antibody which has catalytic activity capable of catalysing degradation of Factor VIII":

It is respectfully submitted that the Examiner might have misinterpreted the invention as claimed, particularly noting "(...) *each teach anti-Factor VIII allo-antibody in at least the abstract*", and his statement that the "*catalytic activity is an inherent characteristic and does not affect the patentability of the product per se*".

In response, it is submitted that the anti-Factor VIII allo-antibodies of the present invention, as claimed in claims 151 and 154, have not been defined in structural terms, since the structure was not available to the inventors at the time of filing this Application, since it is to the best of the Applicant's knowledge that the discovery of catalytic anti-Factor VIII allo-antibodies is the first known disclosure on the emergence of catalytic antibodies that are INDUCED upon treatment of patients with Factor VIII (p.3, l.4 *et seq.* of Application as filed).

Rather, the anti-Factor VIII allo-antibodies of the present invention have been defined in functional terms, *i.e.* anti-Factor VIII allo-antibodies which have catalytic activity which is capable of catalysing degradation of Factor VIII molecules.

It is clear from the description as originally filed (p.3, l.10, *et seq.*) that the catalytic antibodies reported thus far (at the time of filing the Application) in pathological conditions in humans are all auto-antibodies found in the course of disease process or in physiological conditions.

The anti-Factor VIII allo-antibodies of the present invention are respectfully submitted to be new and not anticipated:

i) Preliminary note on terms used:

It is believed that some confusion may be generated by the use of the word "inhibitor". The applicant deems that the Application as published is entirely clear but hereby provides a further definition of the two points:

- Anti-Factor VIII allo-antibodies in patients with hemophilia A "INHIBIT FVIII activity" = these are called "FVIII INHIBITOR".

- We claim peptides that would block/INHIBIT the catalytic activity of anti-Factor VIII allo-antibodies = these peptides are also called "INHIBITOR" or "BLOCKER".

One has to be cautious when reading the text to avoid mistakes and misunderstandings.

ii) *In re.* Prior art documents U, V, W, X, U1, and V1:

Specifically, these prior art documents study anti-Factor VIII antibodies that inhibit Factor VIII in a "classical manner", *i.e.* by simple binding of the antibodies to the molecule and steric hindrance.

These prior art documents do not teach or disclose the CATALYTIC activity of anti-Factor VIII antibodies.

For example, Fulcher proposes that peptides derived from the regions (epitopes) recognized by inhibitory anti-Factor VIII antibodies may be used to block the binding of the antibodies to Factor VIII.

It is the Applicant's understanding that nowhere in the Fulcher document is any teaching or disclosure of an anti-Factor VIII allo-antibody capable of catalysing degradation of FVIII. More particularly, Fulcher NEVER mentions anti-FVIII allo-antibodies capable of catalysing degradation of FVIII. Particularly, in the Fulcher document, p. 7728, right-hand column, fourth full paragraph, line 1 *et seq.*, wherein it is stated "FVIII inhibitors are human autoantibodies or alloantibodies that specifically inhibit the coagulant activity of FVIII".

This sentence from Fulcher's paper addresses "human autoantibodies or alloantibodies that specifically inhibit the coagulant activity of FVIII" by RECOGNITION and BINDING to FVIII. The immunoblot technique used in the paper addresses solely the binding of the antibodies to FVIII and no other mechanism of inhibition of FVIII activity by the antibodies.

Three sentences in Fulcher's document may be responsible for the misunderstanding:

1) Page 7728, last sentence of the Abstract "These data suggest the possibility..."

2) Page 7731, right column, last paragraph, line 6, "they comprise of...on the protein surface".

3) Page 7732, right column, line 2 "The localization of inhibitor epitopes..."

These sentences do not address the mechanism of hydrolysis of FVIII by the allo-antibodies.

The Fulcher document does not even implicitly disclose an anti-FVIII allo-antibody capable of catalysing degradation of FVIII, of claims 151 to 154 of the present patent application: The comments given *infra* should indeed be borne in mind, with respect to the difference between "classical" inhibition and "hydrolytic" or "proteolytic" CLEAVAGE of FVIII.

Claim 151 refers to "an anti-FVIII allo-antibody capable of catalysing degradation of FVIII": *i.e.* anti-FVIII allo-antibodies with catalytic activity to FVIII.

Finally, it is deemed irrelevant to claims 151 to 154 that in Fulcher's document (and many others), it is mentioned that thrombin does hydrolyse/degrade FVIII (for instance, page 7728, right column. FVIII is a natural substrate for thrombin and for Factor IXa).

The present application is submitted to provide a novel mechanism of inhibition of Factor VIII activity, *i.e.* cleavage (*i.e.* "hydrolysis" or "proteolysis") of FVIII by the antibodies which is considered new and is not mentioned in the Fulcher reference.

The present patent application proposes that peptides, or peptide analogues, to the identified cleavage sites, may be used to block the HYDROLYSIS (or "proteolysis") of FVIII by the antibodies.

This notion is not mentioned or contemplated in Fulcher.

Clearly, the subject matter of Fulcher's work and that of the present patent application address two different mechanisms, *i.e.* "classical" inhibition as mentioned above, and "hydrolytic" or "proteolytic" CLEAVAGE, as mentioned above. Therefore, the use of blocking peptides by Fulcher and by the inventors do not concern the same categories of antibodies.

N.B. Although one of the epitopes bound by the antibodies that is described in Fulcher's document is the same sequence as one of the amino acid sequences presently claimed in claim 113:

- Fulcher = Page 7731, right column, last paragraph, line 6: "residues... and 1796-1802): **it is non-isolated and part of a long polypeptide chain**,

- The one of claim 27 is an **isolated** amino acid sequence : Asp Gln Arg Gln Gly Ala Glu.

Furthermore, the mechanism aimed to be blocked is different in the two studies.

A scheme, drawn up by the Inventors as filed herewith clearly shows the invention antibodies and "inhibition".

c) The Examiner's statement that "*claims 117 to 120 are allowed*" is noted. Since it is fully believed that the Examiner's objection with regard to claim 86 has been

overcome, the Examiner's objection with regard to dependent claims 87-105 and 107 (objected to as being dependent upon a rejected base claim) is mooted.

CONCLUSION

In view of the amendments and comments presented herein, favorable reconsideration in the form of a Notice of Allowance is respectfully requested in view of claims 86 to 154.

Should the Examiner believe that a telephonic interview would be beneficial in placing the application in condition for allowance, it is kindly requested that the undersigned representative be contacted.

Respectfully submitted,

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